CORRELATES OF THE DIURNAL PLASMA GLUCOSE VARIABILITY IN NON-INSULIN-TREATED TYPE 2 DIABETIC PATIENTS

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The aim of the study was to identify clinical and biochemical factors modulating glycemic variability in type 2 diabetes (T2DM). We investigated 402 non-insulin-treated T2DM patients (210M/192F), age 57.9±11.2 years, 28 patients on diet only, 168 on monotherapy, 206 on combination therapy. Three daily venous plasma glucose profiles (pre-prandial and postprandial at breakfast, lunch and dinner), HbA1c, fasting total and HDL cholesterol, triglycerides and uric acid levels were obtained. Glycemic variability was evaluated by the standard deviation (SD) and mean amplitude of glycemia excursions (MAGE). Mean postprandial glycemia correlated with age, duration of diabetes and HbA1c. Mean postprandial delta glucose correlated inversely with the total cholesterol, BMI and waist circumference. SD and MAGE correlated directly with the age of the patients and HbA1c, inversely with uric acid levels, but not with duration of diabetes, BMI, total cholesterol, HDL-cholesterol and triglyceride levels. SD and MAGE were the highest in sulfonylurea-treated patients. Age, duration of diabetes, HbA1c and sulfonylurea therapy are possible determinants of larger plasma glucose fluctuations in T2DM. In contrast, obesity and high cholesterol are associated with lower postprandial excursions. Higher uric acid levels are associated with reduced plasma glucose variability.

Key words: Glucose; Diurnal; Pre-prandial; Postprandial; Variability.

INTRODUCTION

It is well known that the majority of type 2 diabetic patients do not fully reach the targets of metabolic control, having higher postprandial plasma glucose levels than recommended[1,2]. Even among patients in apparently good glycemic control according to the glycated hemoglobin (HbA1c) level, postprandial hyperglycaemia is rather common, perhaps because of increased plasma glucose variability throughout the day[3,4]. Starting from the diurnal glucose profiles of the patients we have tried to identify correlates of postprandial hyperglycemia, increased postprandial plasma glucose surge and glycemic variability.

MATERIALS AND METHODS

Patients

A total of 402 patients, 210 men (52.3%) and 192 women (47.7%), mean age 57.9±11.2 years with non-insulin-treated type 2 diabetes mellitus were studied, among them 28 were treated with diet alone, 168 with oral hypoglycemic monotherapy (85 patients with sulfonylurea derivatives and 83 patients with biguanides) and 206 patients were taking combined therapy of two drugs (sulfonylurea and biguanide). All the patients were consecutively recruited from patients hospitalized for medical purposes at the Diabetes Clinic "N. Paulescu" in Bucharest, Romania from January to October 2005.

Diurnal glucose profiles and lab evaluation

Three daily venous blood glucose profiles during a 1-week inpatient period were obtained, including pre-prandial and 2 h postprandial glucose readings for breakfast, lunch and dinner, besides HbA1c (HPLC D-10 Bio-rad) and other important biochemical parameters: fasting total cholesterol, HDL-cholesterol, triglycerides and uric acid levels (Randox Rx-Dytona). The work was approved by the Local Ethical Committee.

Statistics

The data were collected and analyzed by Statistica 6.0. software. Mean pre-prandial and postprandial plasma glucose levels were calculated. Also mean postprandial plasma glucose excursion was computed as mean delta glucose for breakfast, lunch and dinner. To assess the glycemic variability, we used

both the standard deviation (SD) calculation[5]. and the mean amplitude of glycemia excursion (MAGE) calculation[6]. Normality tests were performed to assess the variable distribution. SD values showed a normal (parametrical) distribution and MAGE values showed a non-parametrical distribution. Statistical tests were applied according to the variable distribution. Pearson correlation was computed for normally distributed variables and Spearman correlation was used for non-parametrically distributed variables. A *p* value < 0.05 was considered significant.

RESULTS

Main clinical and biological features of the patients and meal related mean diurnal plasma glucose values are summarized in Table 1.

Table 1

The main characteristics of the patients

	Mean	Median	Std. Dev.
Age (years)	57.9	57.5	11.2
Duration of diabetes (years)	5.89	4.0	5.87
BMI (kg/m^2)	29.3	28.7	5.44
Waist measurement (cm)	101.2	100.0	13.13
HbA1c (%)	8.7	8.4	2.13
Pre-breakfast plasma glucose (mg/dl)	154.9	152.3	37.20
Post-breakfast plasma glucose (mg/dl)	198.1	193.0	58.49
Pre-lunch plasma glucose (mg/dl)	174.1	157.0	64.30
Post-lunch plasma glucose (mg/dl)	172.4	163.0	51.65
Pre-dinner plasma glucose (mg/dl)	155.3	146.3	46.50
Post-dinner plasma glucose (mg/dl)	177.3	173.0	44.93
Delta glucose after breakfast (mg/dl)	42.0	40.0	51.15
Delta glucose after lunch (mg/dl)	5.02	1.75	44.62
Delta glucose after dinner (mg/dl)	21.6	21.0	42.54
All values delta glucose (mg/dl)	23.3	20.5	42.84
Fasting triglycerides (mg/dl)	197.8	148.0	162.08
Fasting HDL-cholesterol (mg/dl)	37.1	36.0	9.01
Fasting total cholesterol (mg/dl)	210.7	209.5	44.08
Fasting uric acid (mg/dl)	5.3	5.2	1.82

We found that mean postprandial plasma glucose level correlated with age of the patients ($r = 0.194$, $p<0.01$), duration of diabetes ($r = 0.121$, $p = 0.022$) and HbA1c ($r = 0.494$, $p<0.01$).

Although pre-meal blood glucose levels (for breakfast, lunch and dinner) were on average quite similar, we found that, for all the patients, the mean delta glucose was mostly increased with breakfast (42 ± 51.1 mg/dl) and dinner (21.6 ± 42.5 mg/dl), but significantly lower following lunch (5.0 ± 44.6 mg/dl), $p < 0.01$ for all comparisons (see Figure1).

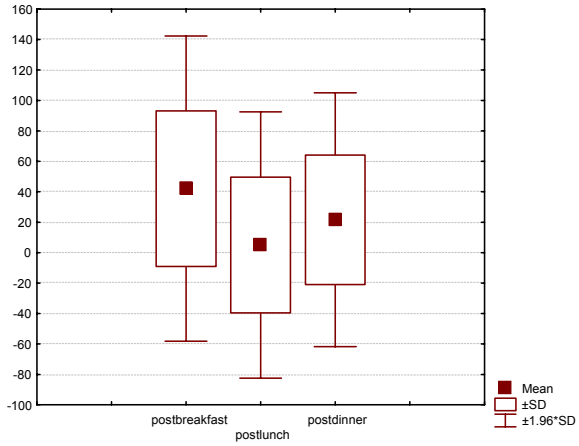

Fig.1. Mean delta plasma glucose following breakfast, lunch and dinner (mg/dl).

We also found that mean delta glucose was significantly but inversely correlated with pre-prandial plasma glucose levels, the correlation coefficient (r value) being -0.341 for breakfast, -0.417 for lunch and -0.373 for dinner (all $p<0.05$).

Mean delta glucose also correlated inversely with total cholesterol level ($r=-0.160$, $p=0.007$), with BMI ($r=-0.118$, $p=0.047$) and waist circumference ($r=-0.129$, $p=0.047$), suggesting a smaller postprandial glycemic surge associated with a more pronounced (particularly abdominal) obesity and higher levels of total cholesterol.

Fasting triglycerides correlated with HbA1c level ($r = 0.196$, $p<0.01$), mean pre-prandial ($r = 0.159$, $p<0.01$) but not with mean postprandial plasma glucose level ($r = 0.080$, $p = 0.114$). Fasting triglycerides correlated also with BMI ($r = 0.224$, $p<0.001$), total cholesterol levels ($r = 0.408$, $p<0.01$), uric acid levels ($r = 0.155$, $p<0.01$) and inversely with age of the patients ($r = –0.2193$, $p<0.01$).

Uric acid levels correlate inversely with mean pre-prandial plasma glucose level ($r = –0.119$, $p = 0,035$) but not with mean postprandial plasma glucose level ($r=-0.070$, $p=0.237$).

Diurnal plasma glucose variability assessed by both SD and MAGE correlated with the age of the patients ($r = 0.209$, $p<0.01$ and $r = 0.189$, $p<0.01$ respectively), and HbA1c ($r = 0.496$, $p<0.01$ and $r = 0.181$, $p<0.01$ respectively), but not with duration of diabetes, BMI, fasting total cholesterol, HDL-cholesterol and triglyceride levels.

Waist circumference correlated inversely with SD ($r = –0.138$, $p = 0.013$) but not with MAGE ($r = –0.121$, $p = 0.053$).

Uric acid levels correlate inversely with both SD ($r = –0.152$, $p<0.01$) and MAGE ($r = –0.165$, $p = 0.014$)

Mean postprandial excursions after lunch and dinner correlated only with MAGE but not with SD. Only mean postprandial excursion post-breakfast correlated both with MAGE and SD (see Table 2).

Table 2

Correlations of SD and MAGE with delta glucose values (postprandial glucose excursions) after breakfast at h10.00 - delta_10, after lunch at h15.00 - delta _15, after dinner at h21.00 - delta_21

	Delta_10	**Delta_15**	**Delta_21**
SD	R = 0.451	R = 0.071	R = 0.092
	P < 0.01	P = 0.449	P = 0.241
MAGE	R = 0.639	R = 0.208	R = 0.319
	P < 0.01	P = 0.026	P < 0.01

No difference regarding postprandial plasma glucose levels, glycemic surge or glycemic variability expressed either by SD or MAGE was encountered between sexes in our study.

When analyzing patients with HbA1c less than 7% ($N = 104$) we found that HbA1c correlated significantly with both MAGE ($r = 0.327$, $p<0.01$) and SD ($r = 0.316$, $p<0.01$). Interestingly, in patients with HbA1c values of 7% or higher ($N = 298$) we found that HbA1c correlated only with SD ($r = 0.417$, $p<0.01$) but not with MAGE ($r = 0.08$, $p = 0.235$).

The diurnal plasma glucose variability as reflected by both SD and MAGE increases as treatment plan is more complex, from the diet-only treated group to the biguanide, sulfonylurea and eventually to the combined therapy group – $p<0.01$ for all group comparisons (see Figure 2).

The least variability expressed by SD is encountered in the diet-only treatment group (26.9 ± 13.5 mg/dl) and the most increased one is found in the combined therapy group (44.7 ± 16.0 mg/dl). Similarly, for MAGE, the lowest value is observed in the diet-alone treatment group (30.5 ± 19.2 mg/dl) and the highest is found in the combined therapy group (51.3 ± 28.3 mg/dl).

When analyzing separately the subgroups of patients on diet-alone vs. non-sulfonylurea therapy vs. sulfonylurea-therapy, there is a gradual and significant increase in diurnal plasma glucose variability as described by both SD and MAGE ($p<0.01$ for all comparisons, see Figure 3) from diet to non-sulfonylurea use and the highest values for SD and MAGE were observed in the subgroup of patients using sulfonylurea, implying that use of these agents alone or in combined therapy in non-insulin-treated type 2 diabetes is associated with the greatest plasma glucose variability.

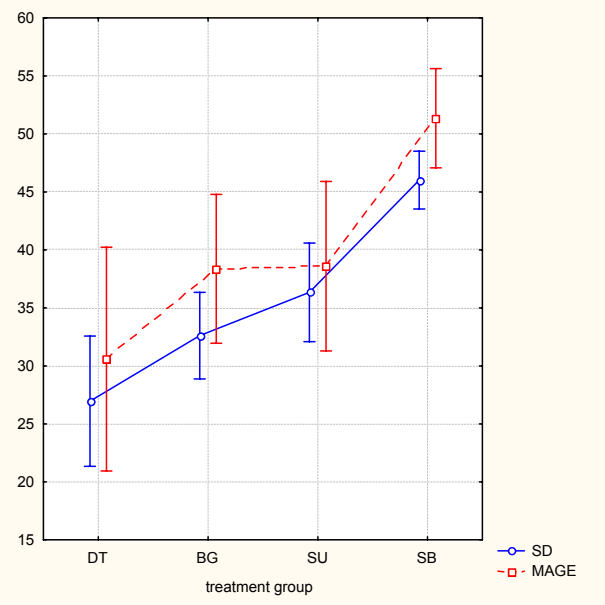

Fig. 2. Increasing glycemic variability in different treatment groups (DT=diet, BG=biguanide, SU = sulfonylurea, SB = sulfonylurea+biguanide) expressed by SD and MAGE (mg/dl).

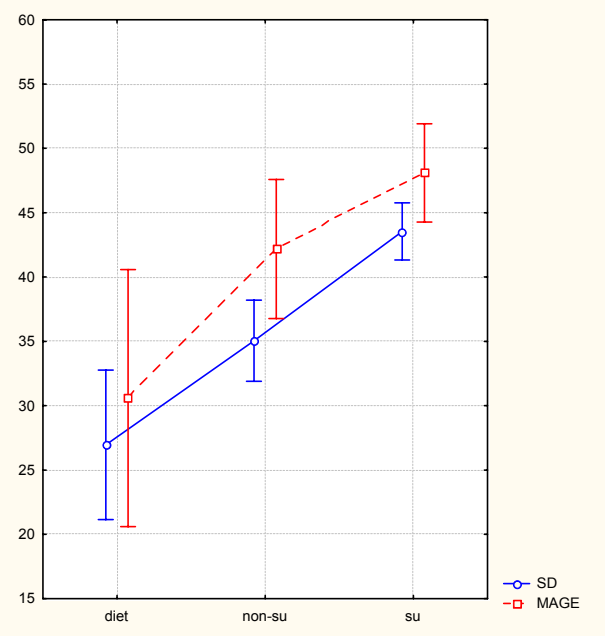

Fig. 3. Increasing plasma glucose variability in patients using oral hypoglycemic agents (non-su = non-sulfonylurea agents, su = sulfonylurea agents) versus diet only-treated type 2 diabetic patients, expressed by SD and MAGE (mg/dl).

During the observation period we found 16 patients, representing 3.98% from the total number (5 women and 11 men) experiencing documented hypoglycemia (plasma glucose < 70 mg/dl) within the diurnal plasma glucose profile. Among these patients, we found HbA1c values less than 7% in 6 patients, values between 7 and 9% in 5 patients and values over 9% in 5 patients. Thirteen patients amongst those with hypoglycemia were treated with sulfonylurea derivatives and the remaining 3 patients were receiving non-sulfonylurea therapy.

DISCUSSION

We conducted the present study in a sample of non-insulin-treated type 2 diabetic patients to identify clinical and biochemical correlates to the elevated postprandial plasma glucose level or 2 h post-meal delta glucose and increased glycemic variability.

As far as we know, there is a small number of studies with series of subjects with type 2 diabetes providing data on daily glucose fluctuations[7-10], and on the other hand the results regarding the significance of glycemic variability for the glycemic control are still subject of debate[11] in type 2 diabetes and even in type 1 diabetic patients where the amount of data is far more extensive [12,13].

However it is obvious from many studies that postprandial hyperglycaemia manifested either as increased values or as increased postprandial glycemic surge is a very frequent phenomenon in patients with type 2 diabetes mellitus. We confirm the data obtained by Bonora et al. who similarly found that mean postprandial plasma glucose level correlated with age of the patients and with the duration of diabetes[8].

Postprandial hyperglycemia is associated with higher HbA1c levels, increased age of the patients and longer diabetes duration.

In contrast with the data published by Bonora *et al.*[8], although the pre-meal blood glucose levels (for breakfast, lunch and dinner) were, on average, quite similar, we found that the delta glucose was mostly increased with breakfast, then significantly lower with dinner and the lowest mean postprandial increase was recorded post-lunch, suggesting a possible dawn-phenomenon influence[14] accompanying the post-breakfast changes in glucose levels, followed by a significant improvement in the glucose tolerance accounting for a second meal effect during lunch[15] and ultimately a dusk-phenomenon explaining the significant increase in mean postprandial glucose after dinner.

The negative correlation of mean delta glucose with BMI, waist circumference and total cholesterol level suggests that leaner and less dyslipidemic patients could manifest a higher mean postprandial glucose excursion as a result of a more insulinopenic phenotype in contrast with the more obese and hypercholesterolemic subjects (in particular having abdominally distributed fat mass) which present with smaller postprandial glycemic surge.

In addition we found that fasting triglyceride levels correlated positively with HbA1c level and mean pre-prandial plasma glucose level, but not with mean postprandial plasma glucose level. High triglyceride levels are associated with poor metabolic control as reflected by the glycated hemoglobin and high pre-prandial glucose, but not necessary with high postprandial glucose as result from the lack of correlation between mean postprandial glucose levels and fasting triglycerides.

Uric acid levels correlated inversely with mean pre-prandial plasma glucose but not significantly with mean postprandial plasma glucose level.

It is obvious that on the background of significant hyperglycemia associating other metabolic abnormalities like hyperlipidemia and hyperuricemia type 2 diabetes patients are exposed to chronic complications due to increased oxidative stress [16,17].

We calculated the variability of venous plasma glucose firstly as the SD around the mean of a six-point glycemic profile measured for each patient during 3 days of observation. One limitation of our study is that with such a methodology, it is probably we have not selected major glucose fluctuations, but rather a composite of both major and minor fluctuations. The second way to analyze the glycemic variability is by MAGE. In contrast with SD, the mean amplitude of glycemic excursions described by Service et al.[6] is designed to quantify major swings of glycemia and to exclude minor ones, since its measurement is obtained by calculating the differences between consecutive peaks or nadirs and includes only those greater than the SD of mean glycemic values.

Ideally, either MAGE or SD can be calculated from the values obtained by CGMS monitoring, but as agreed in literature, both glucose profiles and continuous monitoring gave similar mean glucose profiles and have good associations with HbA1c [18].

As resulting from our data, only 25.8% (104 patients out of the total of 402) were well controlled, presenting with HbA1c value below 7%. In these well controlled patients, both SD and MAGE correlated with the same strength with HbA1c (power calculation p=0.0508 for the difference between the two correlation coefficients). In the poor controlled patients (with HbA1c of 7 % and higher), only MAGE correlated with HbA1c but not SD, suggesting that MAGE would be a more appropriate tool to assess the glycemia variability in this group of patients.

Both SD and MAGE correlated directly with the age of the patients and HbA1c and inversely with uric acid levels.

Waist circumference correlated inversely only with SD but not with MAGE, suggesting that the more obese patients may have a certain pattern of postprandial glucose excursions which is better assessed by the SD value than by the MAGE value.

Regarding the relation of glycemic variability and the post-meal excursions, we observed that only post-breakfast excursion correlated both with MAGE and SD, in contrast with post-lunch and post-dinner excursions which correlated with MAGE but not with SD, implying that higher values for MAGE but not necessarily for SD could signal higher mean postprandial excursions after the main meals.

The highest plasma glucose variability as reflected by both SD and MAGE is found in the combined therapy group and the lowest in the diet-only treatment group. Also higher values for both SD and MAGE were observed in the sulfonylurea-using patients in comparison with the subgroup of patients not using sulfonylurea derivatives.

As resulted from our analysis, the hypoglycemia occurrence during the diurnal profile is more or less evenly distributed across the HbA1c values, the proportion of patients experiencing hypoglycemia being almost similar (6 patients with HbA1c <7%, 5 patients with HbA1c between 7 and 9% and 5 patients with HbA1c > 9%). We could not explain why among the 16 patients with hypoglycemia there were an excess number of male patients, perhaps the number of events is too small to draw certain conclusions.

There are some limitations of our study such as lack of available stored samples for measuring insulinemia, which would have accounted significantly for glucose variations and also the effect of hospitalization in respect to the diurnal glucose variations.

The strengths of the study are the relatively large number of the subjects included, the interest for the plasma glucose variability assessed by both SD and MAGE in type 2 diabetic patients observed during a brief hospitalization and the number of statistically significant correlations between clinical and biological parameters and plasma glucose variability.

CONCLUSIONS

In our study, the highest postprandial plasma glucose value and glycemic surge was encountered post-breakfast. The more obese patients associating hyperlipidaemia (higher fasting total cholesterol and triglyceride levels) and hyperuricaemia demonstrated a reduced postprandial plasma glucose excursion in spite of higher fasting glucose levels.

With increasing age and HbA1c values and decreasing uric acid values, there is higher plasma glucose variability as evaluated by both SD and MAGE. Diet-only treated type 2 diabetic patients demonstrate lower plasma glucose variability in comparison with the patients treated with oral hypoglycemic agents. Use of sulfonylurea agents alone or in combined therapy in non-insulin-treated type 2 diabetes is associated with increased diurnal plasma glucose variability.

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